5,129,723) allegedly because Howie et al. describe a plurality of signal detectors arranged around the flow chamber or arranged to surround the cell. The Office alleges that because Howie et al. describes that the detectors can be placed at any orientation it would have been obvious to one skilled in the art to select the optimum value of the position of the detectors for analysis of a desired scattered radiation.

Applicants contend that Howie et al. does not suggest the invention as claimed. The claimed invention is directed to a sample detection apparatus or flow cytometer having a signal detector placed to selectively detect radiation propagated from the flow chamber at about 54.7 degrees from the direction of polarization of the contacted polarized radiation. The detection apparatus or flow cytometer also can have the opposite orientation where the polarization direction being about 35.3 degrees from the parallel of the sample trajectory and the signal detector being orthogonal to the radiation source. The invention also is directed to a method of detecting fluorescent intensity for a sample in a flow cytometer by detecting radiation emitted from the sample at about 54.7 degrees with respect to the direction of polarization of the radiation.

The application teaches, for example, on page 10, lines 19-32, that radiation from a fluorophore or other molecule is emitted in all directions and whether a fluorophore produces isotropic or anisotropic emission, and to what extent an anisotropic emission will be, depends upon intrinsic properties and mobility of the fluorophore. For example, the application teaches on page 10, lines 21-25, that anisotropic radiation emission from a fluorophore refers to a difference in the amount of radiation emitted in different directions when fluorescence is induced by a polarized source. Isotropic emission refers to the emission of identical amounts of radiation in all directions. The application further teaches on page 10, lines 19 through page 11, line 15, the difficulties associated with fluorescence detection and the associated phenomenon of anisotropic and isotropic emissions. For example, fluorescence intensity measured for an anisotropic sample can change with polarization angle or with the angle of emission such that the intensities measured for the same sample at different angles of detection or for different samples having different degrees of anisotropic radiation emission can be different.

The invention circumvents these inherent variances in fluorescent emissions that can lead to unpredictable results in the measurement of fluorescent intensities by identifying a region where intensity is independent of anisotropic radiation emission. As described, for example, on page 11, lines 15-29, and shown in Figure 2, intensity is independent of anisotropic radiation emission at an angle of about 54.7 degrees from the direction of polarization for radiation contacting the fluorophore. Intensity measurements can be made that are independent of anisotropic radiation emission when, for example, a detector selectively collects radiation that is emitted in a direction of about 54.7 degrees from the direction of irradiation polarization. Alternatively, intensity measurements can be made that are independent of anisotropic radiation emission when, for example, a polarizer with a pass-axis at abut 54.7 degrees from the direction of irradiation polarization is placed in front of a detector.

Similarly, the application further describes, for example, on page 17, line 30 through page 19, line 10, that the polarization of the irradiation beam can be delivered at an angle of about 35.3 degrees from a line parallel to the trajectory of the sample stream. In this regard, the signal detector and illumination beam can be orthogonal with respect to each other or the sample detection apparatus and polarized radiation source can be orthogonal with respect to the sample stream trajectory. Placing either the detector at an angle of about 54.7 or the polarization direction at an angle of about 35.3 results in intensity measurement at an angle independent of anisotropic effects.

Configurations of the signal detector, flow chamber and radiation source orientated at anisotropic-independent angles such as set forth above and described in the application are the geometries claimed in the above-identified application. Similarly, the methods of the invention also employ geometries of the above excitation, sample trajectory and measurement components at anisotropic-independent angles.

In contrast, Howie et al. does not suggest that measurements can be made independent of any anisotropic effect nor does Howie et al. suggest the specific angles of about 54.7 degrees for measurement or of about 35.3 degrees for the direction of polarization. Finally, Howie et al. lacks any suggestion or motivation to product a detection apparatus containing any of the specific geometries claimed by the invention. Instead, Howie et al., appears to describe the measurements of scattered light intensities as a means to derive similar molecular parameters on the basis of a single concentration injected into a chromatographic line. Col. 6, lines 29-32. The measurements are made by an array of detectors arranged in a region that circumscribes the sample flow. Col. 6, lines 33-34. As shown in Figure 3 and further described in Col. 6, lines 43-50, the angle θ at which the scatter is measured is detected relative to the axis of the laser beam. This horizontal placement of detectors and the scatter value measured by Howie et al. is nonanalogous to the claimed invention because there is no suggestion, much less any consideration, of polarization direction nor of detecting radiation emitted at anisotropic-independent angles with respect to the direction of polarization. Instead, Howie et al. is concerned with the measurement of scatter and the application of Snell's Law.

Because Howie et al. does not suggest, and in fact is silent as to measurements of fluorescent emission intensities because Howie et al. is directed to measuring light scatter, the cited reference cannot render the claimed invention obvious. Moreover, because Howie et al. does not suggest, and again is silent as to any placement of fluorescence of detectors at anisotropic-independent angles of about 54.7 degrees from the direction of polarization or placement of the polarization direction at 35.3 degrees from a line parallel to the trajectory of a sample stream, Howie et al. further cannot render the invention obvious. Accordingly, Applicants respectively request that this ground of rejection be withdrawn.

Claims 2-4, 7-9 and 14-17 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Howie et al. in view of Batchelder et al. (U.S. Patent No. 5,037,202). Howie et al. is alleged to describe all the elements of the claims as applied to the independent claims except that it does not describe an arrangement where the sample flow is orthogonal to a detector or radiation source and is parallel to a direction of polarization of the incident radiation. Batchelder et al. is alleged to describe a flow cytometer where the direction of polarization is selectable to include being parallel to the flow trajectory and the sample stream is orthogonal to the radiation source and detection means. Batchelder et al. is further alleged to describe modifications having a selectable polarization states and a plurality of detection means to receive scattered radiation orthogonal to the flow trajectory. The Office Action concludes that it would have been obvious to arrange the components of Howie et al. to achieve the optimum detection conditions and to select the polarization direction and orthogonal arrangements of the radiation source and detection means as claimed allegedly because Batchelder teaches this arrangement.

The rejected claims are dependent claims directed to more specific embodiments where the trajectory of a sample stream is orthogonal to the irradiation source or to a signal detector or where the trajectory is parallel to the direction of polarization.

Batchelder et al. does not cure the deficiencies of the primary references as to either the independent claims from which the rejected depend, nor as to the rejected claims. Batchelder et al. is directed to an optical system for transmitting a focal plane that is useful for classifying particles. Col. 2., lines 44-48. There is no mention of anisotropic effects nor is there a suggestion that measurements independent of this phenomenon would reduce variance in sample measurement. The specific orientations of the radiation source, detection means and direction of polarization allegedly described by Batchelder et al. are therefore irrelevant absent some suggestion of an angle for selectively detecting emitted radiation that is independent of any anisotropic effect because neither the primary reference to Howie et al. nor the secondary reference to Batchelder et al. suggest or provide any motivation to do so. Absent any suggestion, the cited references cannot render the claimed invention obvious. Accordingly, Applicants respectively request that this ground of rejection be withdrawn.

CONCLUSION

In light of the Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call the undersigned attorney.

Respectfully submitted,

Charles L. Asbury et al.

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By: Delbert J. Barnard

Delbert J. Barnard
Registration No. 20,515
Barnard Loop & McCormack LLP
P.O. Box 58888
Seattle, WA 98138
Telephone No. (206) 381-3100
Facsimile No. (206) 381-3101